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A Familial Disorder With Duodenal Atresia and Tetralogy of Fallot

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We report on two sibs with tetralogy of Fallot (TOF) and duodenal atresia (DA). The first child, a 6-year-old girl, had a right facial palsy in addition to the TOF and DA. Her brother, age 10 months, was born with bilateral microtia without facial palsy. The children are the product of an apparently nonconsanguineous union between clinically normal parents. The pertinent family history includes a paternal aunt with TOF and a cleft lip and palate who died in childhood and another paternal aunt with a supernumerary thumb. This family has anomalies found in several syndromes, but does not meet the diagnostic criteria for any of them. The genetic basis for this condition remains unknown, but the pattern of inheritance is likely either autosomal recessive, or autosomal dominant with variable expression and reduced penetrance. The pathogenesis is unknown, but either a disturbance in neural crest cell migration or familial predisposition to vascular disruption might explain this pattern of malformations.

KEY WORDS: familial disorder, duodenal atresia, tetralogy of Fallot, microtia, facial palsy, autosomal inheritance, neural crest, vascular disruption

INTRODUCTION

Tetralogy of Fallot (TOF) and duodenal atresia (DA) are two major, usually isolated malformations that occur sporadically in the population, most of which are likely due to multifactorial determination [Fonkalsrud et al., 1969; Besser, 1990; Best et al., 1990; Graham, 1990]. In addition, both of these embryological defects can arise as part of either a genetic or chromosomal syndrome [Besser, 1990; Graham, 1990]. Isolated DA also appears to segregate in a Mendelian fashion in some families [Best et al., 1989]. Few multiple congenital anomalies syndromes have both TOF and DA as major manifestations [only ten listed in P.O.S.S.U.M., 1994]. In this report we describe two sibs, both with DA, TOF, and craniofacial abnormalities, who appear to be distinct from any previously described syndrome, and discuss the differential diagnosis, the possible genetic basis, and pathogenetic mechanisms for this familial disorder.

CLINICAL REPORTS

Patient 1 (III-1 in Fig. 1, Fig. 2)

Patient 1, currently a 6-year-old girl, was born at 35 weeks of gestational age (GA) by vertex presentation following spontaneous vaginal delivery to a 22-year-old primigravida and her 34-year-old apparently nonconsanguineous husband. The growth parameters at birth were: weight 2,700 g (75–90th centile), OFC 34 cm (75–90th centile), and length 50 cm (>90th centile). The Apgar scores were 8 and 9 at 1 and 5 minutes, respectively.

The pregnancy was complicated by a first trimester urinary tract infection, polyhydramnios in the second trimester, and hyperemesis gravidarum treated with promethazine hydrochloride. The maternal serum α-fetoprotein (MSAFP) level was elevated at 2.9 multiples of the median (MOM) at 16.5 weeks GA and the woman was followed with serial fetal assessments. DA was suspected on ultrasound at 28 weeks GA; genetic amniocentesis was declined. The mother denied any exposure to known teratogens.

At birth the child had an unusual appearance with a complete right facial palsy, a broad nasal bridge, short palpebral fissures, and a short neck. There were no ocular colobomata. She had normal limbs with a left Sydney line. Abdomen and genitalia were normal.

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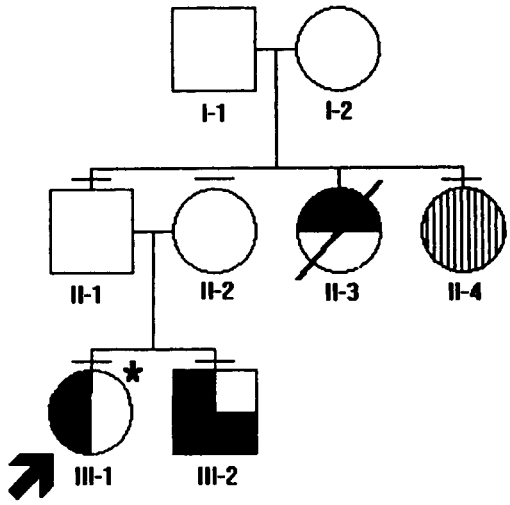

Fig. 1. Pedigree of kinship. ◔, ◪ Tetratology of Fallot; ◔, ◪ duodenal atresia; ◍ supernumerary thump; ◪ microtia; ◔ cleft lip and palate; ○* facial palsy; ○, □ personally examined; ↗ proposita.

Shortly after birth, the patient had endotracheal intubation because of a sudden onset of cyanosis. Auscultation demonstrated a loud murmur and an echocardiogram showed the presence of TOF, hypoplastic pulmonary arteries, and a patent ductus arteriosus. She underwent a right Blalock-Taussig shunt on day 2 of life. On day 10, the patient had a duodenoduodenostomy for repair of a type III DA. Type III DA have no connecting fibrous cord between the blind ends of the bowel [Besser, 1990].

Chromosome analysis showed a normal female karyotype (46,XX) at >400 band resolution. No deletion on the long arm of chromosome 22 was detected by fluorescent in situ hybridization (FISH) studies using the DiGeorge probe (D22S75). Results of the cranial ultrasound study and an ophthalmological examination were normal. Brainstem auditory evoked response showed no evidence for involvement of the eighth cranial nerve. Calcium levels were normal.

The patient was discharged on day 42 on spironolactone-hydrochlorothiazide and digoxin. At age 4 years, she underwent definitive repair of her cardiac defect. Presently she does not need any cardiac medication.

The patient has always been small. Her height and OFC have followed the 25th centile, but her weight was consistently at or below the 5th centile until after the second heart operation. At her last visit, her growth parameters were height 115.2 cm (50–75th centile), weight 22.5 kg (75–90th centile), and OFC 50.4 cm (25–50th centile). Psychomotor development was normal. The patient twice was assessed developmentally. Her adaptive and motor skills were consistent with her chronological age. Her language was progressing, albeit at a slightly slower pace. At age 6, she is in good health and doing well in an age-appropriate grade in school.

Patient 2 (III-2 in Fig. 1, Fig. 3)

The second child, a boy, was born normally at term following induction of labor. Apgar scores were 9 at both 1 and 5 minutes. The physical parameters at birth were as follows: OFC 31 cm (10th centile), length 48 cm (50–75th centile), and weight 2,705 g (25–50th centile).

This pregnancy was complicated by hyperemesis gravidarum requiring treatment (doxylamine-pyridoxine

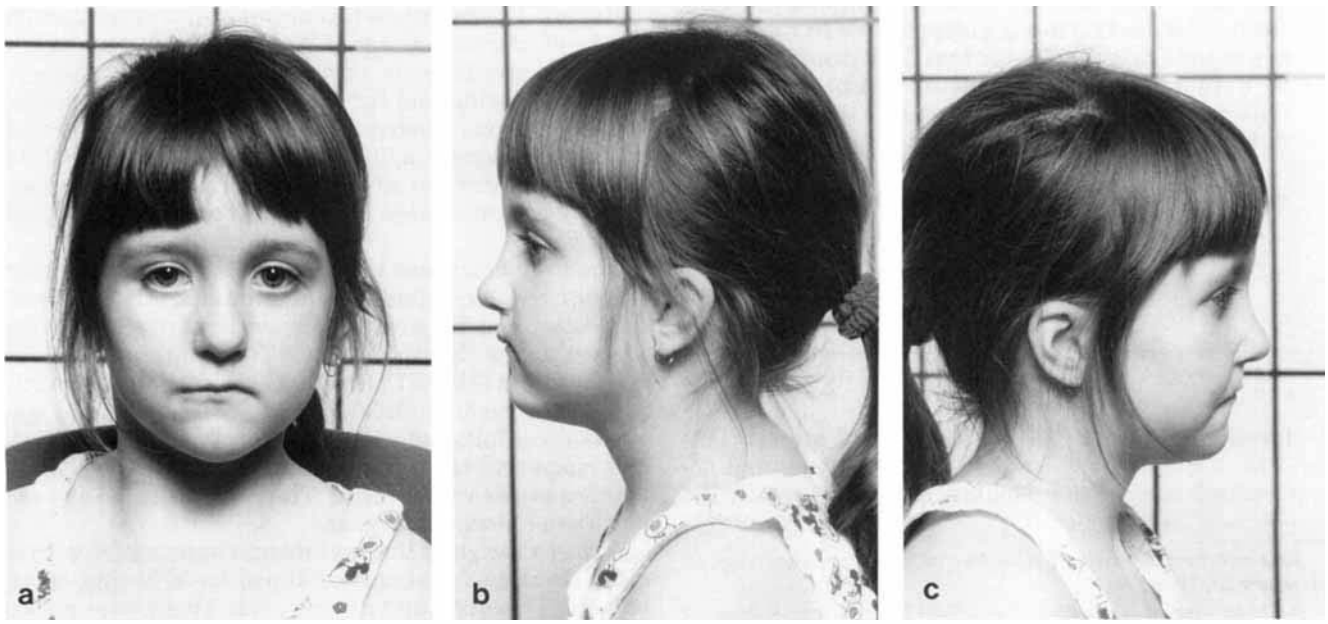

Fig. 2. **a, b, c:** Front and side views of patient III-1 in Figure 1. Note mild right facial palsy.

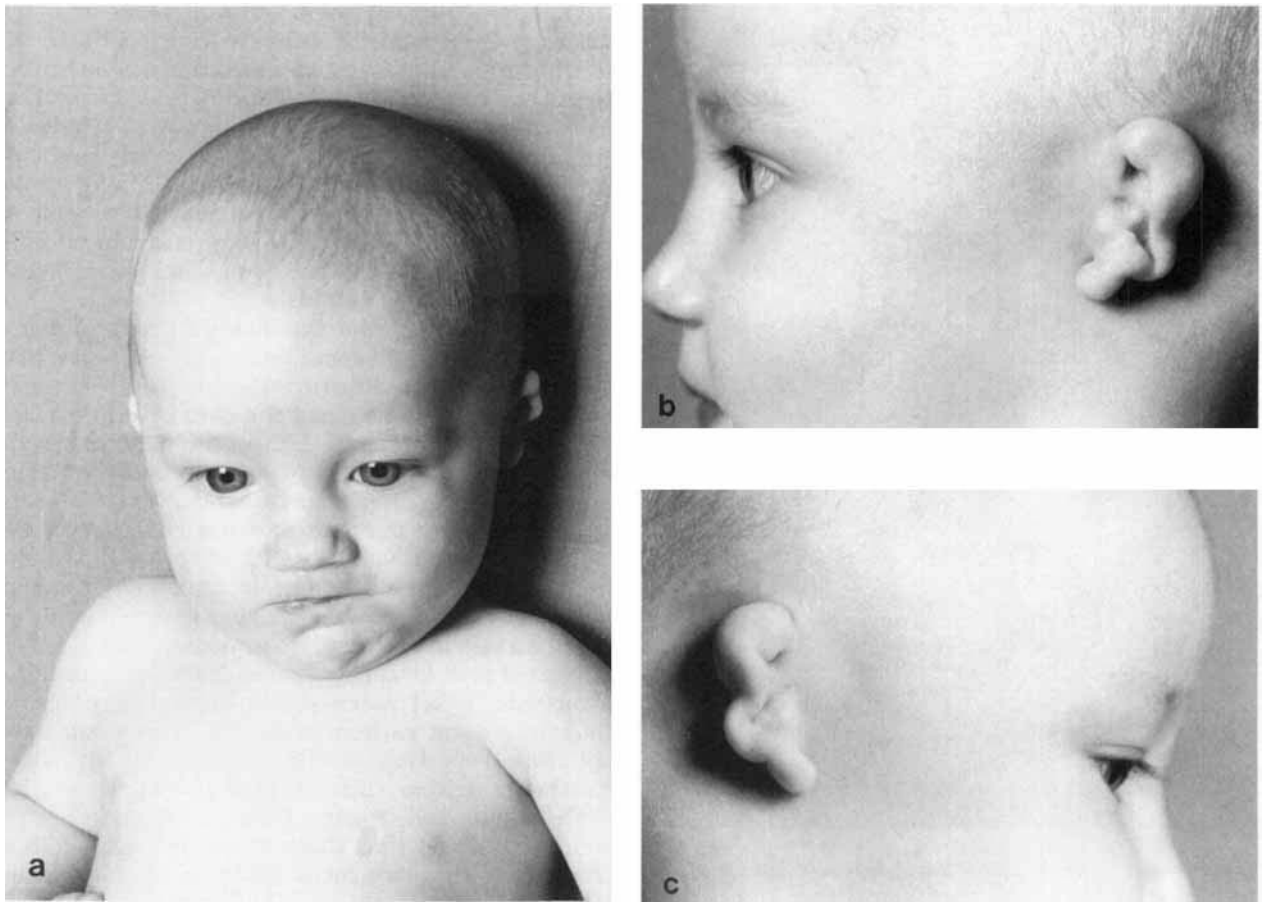

Fig. 3. **a, b, c:** Front and side views of patient III-2 in Figure 1. Note bilateral microtia.

HCl) and polyhydramnios in the third trimester. DA and TOF were both suspected on fetal ultrasonographic examination at 18 weeks and confirmed at 24 and 30 weeks, respectively. A cordocentesis at 25 weeks GA indicated a normal male karyotype (46,XY) at <400 band resolution. The MSAFP level was normal (1.0 MOM at 17 weeks GA). The mother denied any exposure to known teratogens.

At birth, bilateral microtia with absence of external ear canals was noted (Fig. 3). An echocardiogram confirmed the antenatal diagnosis of TOF, but there was no cyanosis and no need for early cardiac intervention. The patient was operated on day 2 of life for a type I DA. Type I DA have an intact membrane separating the markedly enlarged proximal segment from the smaller distal portion [Besser, 1990]. Intestinal malrotation was detected and also repaired. Post-operatively, his hospital stay was complicated by hyperbilirubinemia and a *S. aureus* cellulitis and septicemia secondary to a central line infection. Following a course of intravenous antibiotics, the patient was discharged on day 19. Calcium levels were found to be normal.

A brainstem auditory evoked response showed intact peripheral auditory pathways with signs suggestive of significant central auditory impairment. A CT scan of the middle ear showed bilateral external canal aplasia with ossicular abnormalities and intact inner ear anatomy. The cardiac defect was repaired at age 7 months. At 9 months he was fitted with a bone conduction hearing aid.

He has not been formally assessed with respect to his development, but his mother feels that he is less behind than his sister at that same age. At 11 months he is sitting independently and walking with assistance. His speech consists of single words and a speech therapist is monitoring his progress.

Family History

The family history is remarkable in that a paternal aunt was born with a cleft lip and palate and TOF (II-3 in Fig. 1 and Fig. 4). She died at age 9 years during cardiac surgery. No ear anomalies were present on review of photographs. A second paternal aunt was born with a supernumerary thumb (II-4). No other anomalies were present. There is no consanguinity between the paternal grandparents. Both parents are clinically normal. The father has normal cardiovascular anatomy and function as judged by an echocardiogram and normal hand radiographs (II-1). The mother was adopted and her family history is unknown (II-2).

DISCUSSION

We present two sibs with an apparently previously unreported familial condition characterized by anom-

Fig. 4. Patient II-3 in Figure 1. Note family resemblance and repaired cleft lip.

alies affecting the heart, the gut, and craniofacial structures. Both affected individuals had TOF and DA. Individual III-1 had a right facial palsy, while individual III-2 lacked the facial palsy but had bilateral microtia with no external canals. Chromosomes were normal in both children.

The differential diagnosis includes CHARGE. CHARGE is an acronym for a collection of clinical findings: **C**oloboma, **H**eart defect, **A**tresia choanae, **R**etarded growth and development, **G**enital hypoplasia and **E**ar anomalies [Hall, 1979; Oley et al., 1988]. The diagnosis of CHARGE requires four of seven criteria one of which must include either choanal atresia or coloboma [Oley et al., 1988]. Both patients have TOF, the most common heart defect seen in CHARGE patients [McKusick, 1992]. One patient (III-1) has a facial palsy, a frequent clinical finding in CHARGE and the other (III-2) had ear anomalies. However, microtia is not a characteristic ear abnormality in CHARGE [Oley et al., 1988]. Neither patient meets the diagnostic criteria of CHARGE. In addition, the patients have DA, a feature not seen in CHARGE. FISH studies using the DiGeorge probe (D22S75) failed to detect a deletion in 22q. Some CHARGE patients have a microdeletion in the 22q11.2 region [Emanuel et al., 1992; McKusick, 1992]. It is estimated that as many as 5% of newborn infants with congenital heart defects have a detectable 22q deletion using FISH studies and the DiGeorge probe [Glover, 1995].

The possibility of some other microdeletion elsewhere in the genome or a cryptic translocation leading to the observed clinical manifestations in our two patients has been considered. The fact that the phenotypically normal father has potentially two affected sisters (II-3 and II-4 in Fig. 1) makes this scenario less plausible. However, we cannot rule out the possibility that the father is a gonadal mosaic for a contiguous gene syndrome consisting of TOF, DA and craniofacial abnormalities and that the father's two sisters have birth defects unrelated to the children.

Also considered was the Townes-Brocks syndrome (TBS), an autosomal dominant condition characterized by malformations affecting the gastrointestinal (GI) tract, the upper limbs, and the ears [Aylsworth, 1990; O'Callaghan and Young, 1990]. The most common GI manifestations in TBS are anal stenosis, anteriorly placed anus or imperforate anus, none of which were present in our two patients [Aylsworth, 1990; O'Callaghan and Young, 1990]. Silver et al. [1972] reported three patients with radial anomalies, congenital heart defects, and other malformations, including duodenal atresia in one case. He considered these to be examples of Holt-Oram syndrome. However, Monteiro de Pina-Neto [1984] proposed that these three cases more likely represent patients with TBS. This would extend the clinical spectrum of TBS to include DA and congenital heart defects such as TOF [König et al., 1990; O'Callaghan and Young, 1990]. However, there are some who doubt that these cases represent TBS and think that they are more likely in the spectrum of VACTERL. This distinction is of some relevance to this family since one paternal aunt (II-4) had a supernumerary thumb, a defect seen in TBS. However, neither child nor their parents have radial ray anomalies and, to our knowledge, no TBS patients have had both DA and TOF. Hand films of the father, the presumed transmitting parent (assuming autosomal dominant inheritance), were clinically normal.

A syndrome of anotia, facial palsy and cardiac anomaly has been reported which describes the coexistence of these three defects in the absence of exposure to thalidomide. Two case reports on three patients have appeared in the literature [Matthies, 1966; Pearl, 1984]. In this condition, the ear anomalies ranged from preauricular skin tags to microtia/anotia. Two of the three cases had heart defects that were variations of TOF (VSD and pulmonary stenosis). The facial palsy affected the entire side of the face with ptosis. In the case reported by Matthies [1966], the facial paralysis was shown to be secondary to the congenital absence of the right facial nerve on autopsy. In our family, only patient III-1 had a facial palsy and this has improved with time. An electromyogram and nerve conduction studies showed findings consistent with either a lesion in the right seventh cranial nerve without denervation and/or congenital poor development of facial musculature. This is different from the post-mortem finding in the case described by Matthies [1966]. None of the three patients with this syndrome had DA, which makes this syndrome an unlikely diagnosis in our family.

Kawashima et al. [1987] reported on three cases of a syndrome of microtia and aortic arch anomalies. The findings in this condition were reminiscent of DiGeorge syndrome with interrupted aortic arch, malformed ears with or without obstruction of the external ear canal, and micrognathia. The patients had normal serum calcium levels and normal lymphocytes. One patient presented with a left unilateral facial palsy. DA and TOF were not reported as part of this condition and therefore we doubt that our patients have this syndrome.

The family in this report appears not to match any previously described syndrome. We suggest that this condition is a newly recognized familial disorder with DA, TOF and craniofacial abnormalities as major manifestations. The genetic basis of this condition remains unclear. Based on the family history, this could be an autosomal dominant disorder with variable expressivity and reduced penetrance. The two paternal aunts, one with TOF and cleft lip and palate and the other with a supernumerary thumb may represent variable expression of the same autosomal dominant mutation. If that is the case, the clinically normal father would represent a case of non-penetrance.

Another possibility is that the two sibs represent an autosomal recessive condition with TOF and DA manifesting in a family with a predisposition to TOF (II-3) and other anomalies (supernumerary thumb, microtia and facial palsy). Alternatively, the DA could be inherited in an autosomal recessive fashion in a family at high risk for TOF. Two of us (A.E.C., N.E.W.) have previously reported familial cases of isolated DA where inheritance appears to be autosomal recessive [Best et al., 1989]. We have presumed that this couple are non-consanguineous, but the fact that both parents are Caucasians and the mother was adopted and her family history is unknown precludes us from knowing this with certainty.

The finding of TOF and DA in two sibs may simply reflect chance concordance in which two anatomical defects have arisen by different pathogenetic mechanisms in a family already predisposed to TOF. However, it is interesting to speculate that the constellation of anomalies in the sibs have some common pathogenetic basis such as a disturbance in neural crest cell migration or familial predisposition to vascular disruption.

Neural crest cells play a major role in the embryogenesis of branchial arch structures and in the septation of the cardiac outflow tract [Siebert et al., 1985; Kirby and Waldo, 1990]. Microtia, facial palsies and TOF may reflect heterogeneous clinical manifestations of neurocristopathies [Siebert et al., 1985; Kirby and Waldo, 1990]. Abnormal migration of neural crest cells destined for the enteric plexus is the pathogenic basis of Hirschsprung disease [Passarge and Stevenson, 1993]. Foregut anomalies such as duodenal atresia and stenosis have been observed in cases of suspected neurocristopathies; however their relationship to neural crest cells is unknown [Buckfield et al., 1971; Siebert et al., 1985; Voisin et al., 1987; Mooy et al., 1990].

Two mechanisms have been proposed to explain the pathogenesis of duodenal atresia. The favored mechanism is that of failure of re-canalization of the duodenal lumen, but vascular disruption has also been considered [Best et al., 1989]. Vascular disruption is favored as a cause of small intestinal atresias distal to the duodenum [Best et al., 1989; Cragan et al., 1993]. Nevertheless, our patient 2 had an intestinal malrotation detected at the time of surgery. This has been invoked as a contributing factor in small bowel atresias [Cook and Bennett, 1995]. In keeping with the vascular hypothesis are the other vascular disruption defects including renal agenesis, porencephalic cyst and horseshoe kidney that have been reported in association with duodenal atresia in newborn infants [Van Allen, 1992; Cragan et al., 1993]. Microtia and facial nerve palsy, each seen in one of our cases, is thought to arise from a vascular disruption etiology [Van Allen, 1992].

Evans and Czeizel [1995] described a case where a male child had duodenal stenosis, TOF, tracheal agenesis, right radial aplasia, aberrant right subclavian artery, hydroureter, and polysplenia. Vascular defects resulting from a primary defect in blastogenesis were suggested as a mechanism for the limb and potentially other defects in this infant.

Robinow et al. [1986] described a heterogeneous autosomal dominant condition in two families with combinations of hemifacial microsomia, facial nerve palsy, and ear anomalies. One individual in family B had microtia with atresia of the auditory meatus, mild right hemifacial microsomia and a conotruncal heart defect (either pulmonary atresia with a ventricular septal defect or transposition of the great vessels). Chromosome studies showed a normal 46,XY karyotype.

In summary, this family represents a newly described pattern of anomalies that, at present, does not permit us to assign a specific genetic basis. We hope additional cases will be reported in the future which might help us elucidate the mode of inheritance of this disorder. Abnormalities in neural crest cell migration or vascular disruption are both plausible pathogenic mechanisms.

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